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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/766,057 | 01/28/2004 | Roy H. Larsen | 50147/003002 | 2306 |

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| EXAMINER | |
|---|---|
| PERREIRA, MELISSA JEAN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1618 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 04/09/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/766,057 | LARSEN ET AL. | |
| | Examiner | Art Unit | |
| | MELISSA PERREIRA | 1618 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *18 and 25-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18 and 25-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/13/09 has been entered.

### *Previous Claims and Rejections Status*

2. Claims 18 and 25-35 are pending in the application.

3. The rejection of claims 18 and 25-35 under 35 U.S.C. 103(a) as being unpatentable over Niswender (US 4,336,185) in view of Wedeking et al. (US 6,093,382) and further in view of Sinkule et al. (EP 282057) is withdrawn.

4. The rejection of claims 18,25-28 and 30-35 under 35 U.S.C. 103(a) as being unpatentable over Niswender (US 4,336,185) in view of Wedeking et al. (US 6,093,382) and further in view of Goldenberg et al. (US 5,698,178) is withdrawn.

### *New Grounds of Rejection*

### *Claim Rejections - 35 USC § 103*

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 18 and 25-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wedeking et al. (US 6,093,382) in view of Sinkule et al. (EP 282057).

7. Wedeking et al. (US 6,093,382) discloses the method of preparing a diagnostic/therapeutic gadolinium-folate (folic acid) conjugate and the method of targeting the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate to a tumor cell expressing FBP (folate binding protein) (i.e. malignant cells) which involves administering the conjugate to a mammal and monitoring the biodistribution (column 1, lines 8-50; column 6, lines 28+; column 7, lines 21-28 and 48-59; column 8, line 44-59; column 10, lines 18-25; column 68, lines 31+; example 17). The compound of column 51-52 contains multiple folates (folic acid) conjugated to a radionuclide chelator capable of binding gadolinium. FBP is frequently strikingly elevated in a variety of carcinomas and thus allows for selective concentration of pharmaceutical or diagnostic agents in tumor cells, such as ovarian cancer relative to normal cells (column 3, lines 25-35; column 4, lines 37-54; column 5, lines 1-7). The monomeric folate conjugates of Gd chelates designed for use in MR applications indicate that structural modifications that bring about an increase in the intensity of the MR signal are advantageous, as the signal intensity obtainable with this technique is determined by the quantity of paramagnetic or superparamagnetic metal that can be localized in the target tissues which is limited by the quantity of folate binding protein present in those tissue (column 7, lines 21-38). Wedeking et al. does not disclose the coupling of an antibody to the folate gadolinium-folate (folic acid) conjugate.

8. Sinkule et al. (EP 282057) discloses the method of monitoring the biodistribution of a receptor binding conjugate comprising three components, 1.) a monoclonal antibody, IgG (column 2, lines 30-31; example 4), 2.) a radionuclide (column 3, lines 39-55; column 17, lines 5-17) a chemotherapeutic agent, such as folate analogues and multiples thereof (abstract; column 2, lines 11-14 and 29-30; column 4, lines 18-28) via the administration to a mammalian (i.e. intravenous) (column 6, lines 19+). The method of linking the folic acid derivative to an antibody involves conversion of the folic acid derivative to the activated ester (mixed anhydride) with acetic anhydride and mixing it with the antibody (column 8, lines 40-44). The antibody-folic acid derivative product is further attached to a radionuclide (column 6, lines 22-25). The antibody may be a monoclonal, polyclonal or variations thereof used for a wide variety of target antigens (column 3, lines 56+; column 4, lines 9-15), such as (443A6) which recognize a 40k dalton epithelial antigen found on human breast adenocarcinomas (column 8, lines 33-39; example 3). The targeting antibodies are included in the conjugate to target the conjugate to a desired tumor cell for uptake with a high degree of specificity which facilitates the destruction of cancerous cells while minimizing the damage to normal cells (column 5, lines 9-12 and 22-47) an the choice of antibody will depend on the type of cancer with which the patient is afflicted (column 5, lines 40-47).

9. At the time of the invention it would have been obvious to one ordinarily skilled in the art to attach an antibody, such as the IgG of Sinkule et al. to the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate of Wedeking et al. to target the conjugate specifically to a desired type of cancer cells/target. FBP is

expressed in normal as well as different tumor cells and thus it would be advantageous to attach an antibody to the conjugate of Wedeking et al. to ensure site-specific targeting of the conjugate into the desired tumor cells with enhanced affinity while minimizing the damage to normal cells.

10. Claims 18 and 25-28 and 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wedeking et al. (US 6,093,382) in view of Goldenberg et al. (US 5,698,178).

11. Wedeking et al. (US 6,093,382) discloses the method of preparing a diagnostic/therapeutic gadolinium-folate (folic acid) conjugate and the method of targeting the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate to a tumor cell expressing FBP (folate binding protein) (i.e. malignant cells) which involves administering the conjugate to a mammal and monitoring the biodistribution (column 1, lines 8-50; column 6, lines 28+; column 7, lines 21-28 and 48-59; column 8, line 44-59; column 10, lines 18-25; column 68, lines 31+; example 17) as well as that stated above. Wedeking et al. does not disclose the coupling of an antibody to the folate of the gadolinium-folate (folic acid) conjugate.

12. Goldenberg et al. (US 5,698,178) discloses the method of selectively targeting diagnostic and therapeutic agents to multidrug resistant cells via administration of receptor binding conjugates (column 4, lines 1-11; column 5, line 56+; column 23, lines 1-10). The receptor binding conjugates comprise various antibodies, such as IgG and IgM (column 4, lines 21-34; column 20, lines 54+), at least one diagnostic or therapeutic

agent, such as radionuclides (abstract, column 4, lines 35-56; column 20, lines 39-53; column 23, lines 11+) and cancer chemotherapeutic drugs, such as folic acid analogues (column 23, lines 55-57). The antibodies used for targeting provides for the clearance of a nontargeted circulating radiolabeled antibody. Humanized antibodies may be used as an equivalent to other antibodies for targeting a desired site and obviates potential problems associated with the immunogenicity of murine constant regions (column 10, line 17+; column 12, lines 4-13).

13. At the time of the invention it would have been obvious to one ordinarily skilled in the art to attach an antibody, such as the IgG of Goldenberg et al. to the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate of Wedeking et al. to target the conjugate specifically to a desired type of cancer cells/target. FBP is expressed in normal as well as different tumor cells and thus it would be advantageous to attach an antibody to the conjugate of Wedeking et al. to ensure site-specific targeting of the conjugate into the desired tumor cells with enhanced affinity.

### *Response to Arguments*

14. Applicant's arguments filed 2/13/09 have been fully considered but they are not persuasive.

15. Applicant asserts that Wedeking et al. does not describe or suggest conjugates containing a folate and an antibody or antibody fragment.

16. The reference of Wedeking et al. was not used to teach of the conjugate containing a antibody but used to teach that the diagnostic/therapeutic gadolinium-folate

(folic acid) conjugate is targeted to tumor cells expressing FBP (folate binding protein) (i.e. malignant cells). Sinkule et al. was used to teach of the coupling of an antibody to a folate analog-antibody-radionuclide conjugate. FBP is expressed in normal as well as different tumor cells and thus it would be advantageous to attach an antibody as taught by Sinkule et al. to the conjugate of Wedeking et al. to ensure site-specific targeting of the conjugate into the desired tumor cells with enhanced affinity while minimizing the damage to normal cells.

17. Applicant asserts that Sinkule et al. describes that the chemotherapeutic agent, folic acid analog must be clinically useful against malignancies and pathological states and in contrast, applicant's claims require the folate to be non-cytotoxic. Sinkule et al. teaches away from using a non-cytotoxic folate in a conjugate containing an antibody or antibody fragment and a radionuclide.

18. The reference of Sinkule et al. was not used to teach of a non-cytotoxic folate but used to teach of the coupling of an antibody, such as IgG to the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate of Wedeking et al. which is targeted to cells expressing FBP. FBP is expressed in normal as well as different tumor cells and thus it would be advantageous to attach an antibody as taught by Sinkule et al. to the conjugate of Wedeking et al. to ensure site-specific targeting of the conjugate into the desired tumor cells with enhanced affinity while minimizing the damage to normal cells.

19. Applicant asserts that the synthesis of conjugates containing an antibody, a radionuclide and a non-cytotoxic folate while maintaining the targeting ability of both the

antibody and folate components, is more difficult than the synthesis of conjugate containing only a radionuclide and either an antibody or a non-cytotoxic folate.

20. The instant claims recite the, "step of coupling said antibody to said at least one-cytotoxic folate is carried out by means of an activated ester". The reference of Sinkule et al. teaches that the method of preparing the folic acid derivative-antibody bond involves conversion of the folic acid derivative to the activated ester (mixed anhydride) with acetic anhydride (column 8, lines 40-44) and further attaching a radionuclide to the conjugate (column 6, lines 22-25). Therefore it would have been obvious to one skilled in the art to prepare an activated ester of the folic acid of Wedeking et al. and thus the coupling of the antibody of Sinkule et al. to the folic acid-radionuclide conjugate of Wedeking et al. via an activated ester would be predictable.

21. Applicant asserts that Goldenberg et al. describes that the folic acid analog must function as a chemotherapeutic agent, and therefore, are cytotoxic. A non-cytotoxic folate as recited in the present claims would not have this function. Applicant submits that one skilled in the art, in view of Goldenberg, would not be motivated to combine an antibody (or antibody fragment) with a radionuclide and a non-cytotoxic folate as required by the present claims.

22. Goldenberg et al. was not used to teach of a non-cytotoxic folate but used to teach of the coupling of an antibody, such as IgG to the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate of Wedeking et al. which is targeted to cells expressing FBP. FBP is expressed in normal as well as different tumor cells and thus it would be advantageous to attach an antibody as taught by Goldenberg et al. to the

conjugate of Wedeking et al. to ensure site-specific targeting of the conjugate into the desired tumor cells with enhanced affinity.

***Conclusion***

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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